PENICILLINS — NEW INSIGHTS INTO THEIR MECHANISMS OF ACTIVITY AND CLINICAL USE

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INTEREST has increased during the past decade in how penicillins inhibit bacteria and in clinical situations for which they remain the drugs of first choice although many other drugs have been discovered. This has resulted from increased understanding of the biochemical activity of these compounds and increased awareness of the value of these agents as essential in the chemotherapy of both immunocompromised patients and patients in outpatient settings. I shall attempt to review in brief our current understanding of the biochemical activity of penicillins, the mechanisms of resistance of bacteria to penicillins, and then focus in some detail on the use of the broad spectrum penicillins which inhibit such Gram-negative bacilli as *Pseudomonas aeruginosa*, which are such important pathogens in patients with depressed host cell defenses.

MECHANISM OF ACTION

To understand how penicillins inhibit bacteria, it is essential to have at least a cursory knowledge of how a bacterial cell wall is formed and why bacteria need cell walls. Bacteria utilize their cell walls to maintain their shape, but, more important, cell walls are an osmotic barrier by which bacteria keep certain molecules outside themselves and by which they are able to retain nutrients and the building blocks for protein and nucleic acids in the cell. Gram-positive species have an internal osmotic pressure approximately 10 to 30 times the external milieu, whereas Gram-negative species and enterococci have an external pressure three to five times the external environment. The rigid aspect of the bacterial cell wall is due to linear polysaccharide chains which are cross-linked by short peptide

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TABLE I. I_{50} BINDING TO PENICILLIN-BINDING PROTEINS*

Compound	*Proteins of E. coli*			
	Ia	*Ibs*	*2*	*3*
		μg./ml.		
Penicillin G	0.5	3	0.8	0.9
Ampicillin	1.4	3.9	0.7	0.9
Cloxacillin	2	23	15	3
Carbenicillin	2.1	5	4	2.1
Mezlocillin	1.5	8	0.9	0.025
Mecillinam	>250	>250	0.25	>250

*The concentration of drug which will cause a 50% reduction in the binding of ^{14}C benzylpenicillin. The lower the number, the greater affinity a compound has for a penicillin-binding protein.

segments. This part of the wall is the peptidoglycan or murein sacculus of the bacterial cell. Many enzymes, perhaps in excess of 30, are involved in making this murein layer, but the final aspect of the cross-linking occurs outside the cytoplasmic membrane of both Gram-positive and negative bacteria and it is this final aspect that is inhibited by β-lactam antibiotics. The best concept about the nature of the action of penicillins upon bacteria was provided in 1965 by studies of Tipper and Strominger,[1] who showed that penicillin indeed inhibited the cross-linking of peptidoglycan of *Staphylococcus aureus* because penicillin prevented removal of the terminal D-alanine of the peptide that linked the chains. Indeed, they suggested that penicillin might function as a structural analogue of acyl-D-alanyl-D-alanine.

However, our real understanding of the activities of the penicillins was associated with the detection and purification of proteins that interact with penicillin, the penicillin-binding proteins (PBPs) (Table I).[2] Purification of these proteins has been a real achievement because the proteins constitute only 1% of the membrane-bound protein. Early studies of the action of penicillin on such Gram-negative species as *Escherichia coli* did not show lysis such as occured with *S. aureus*, but a lengthening of the bacterial cells. As new penicillins were discovered, different types of effects were seen. For example, with ampicillin there was a bulge in the center of the bacterial cell, and a drug such as amoxicillin caused a bulge in the center of the cell and then a burst with lysis. A drug such as mecillinam, to be discussed later, caused only formation of osmotically stable spheres that could actually divide and continue as spheres for many generations if mecillinam were present in the medium.

Spratt[2] analyzed the various proteins in bacteria which bind penicillins and correlated PBP binding with morphologic changes. He showed that there were three proteins, PBPs lb, 2, and 3, that were the primary target of β-lactams (penicillins and cephalosporins), and that inactivation of any one of these targets was a potentially lethal event for the bacteria. The greater affinity a compound had for one of these penicillin-binding proteins, the lower the concentration at which the organism would be inhibited and for practical purposes killed. Gram-positive bacteria have different PBPs so that an agent could bind well to the PBPs of Gram-negative bacteria and not to the PBPs of Gram-positive or vice versa to explain in part some of the differences in activity of penicillins against Gram-positive and negative bacteria (Figure 1).[4]

Although sites exist to which penicillins bind, the penicillin compound has to get to the PBP site, that is, the compound must reach the outer aspect of the cytoplasmic membrane which is below the outer parts of the cell wall. In certain organisms, such as the Gram-negatives, there is another complication, namely, enzymes situated in the periplasmic space of the bacteria which guard and protect the receptor proteins by destroying entering penicillins.[4]

Resistance of Bacteria to Penicillins

Understanding the sites to which penicillins must bind and that the penicillin must reach the receptor without being destroyed provides a basis for a comprehension of bacterial resistance to the compounds. The first form of resistance recognized was that of penicillinases. By 1946 fewer than 25% of *S. aureus* found in hospitals in Great Britain and the United States were susceptible to penicillin G.[5] This was due to the selection within hospitals of isolates of *S. aureus* that possessed a penicillinase (β-lactamase) which ultimately was shown to be due to the presence of a plasmid (extra-chromosomal piece of DNA) which mediated the synthesis of the enzyme. By 1967 resistance of *S. aureus* to penicillin in the community had reached levels of 70% and was 90 to 95% in hospitals.[5]

But this resistance was to a great extent overcome by the synthesis of semisynthetic penicillins, the first of which was methicillin.[6] This compound resisted hydrolysis by staphylococcal β-lactamase. In recent years staphylococci resistant to compounds such as methicillin, oxacillin, and nafcillin have appeared. These organisms had appeared worldwide in the mid 1960s,[5] but vanished until the past year, when analysis of hospital

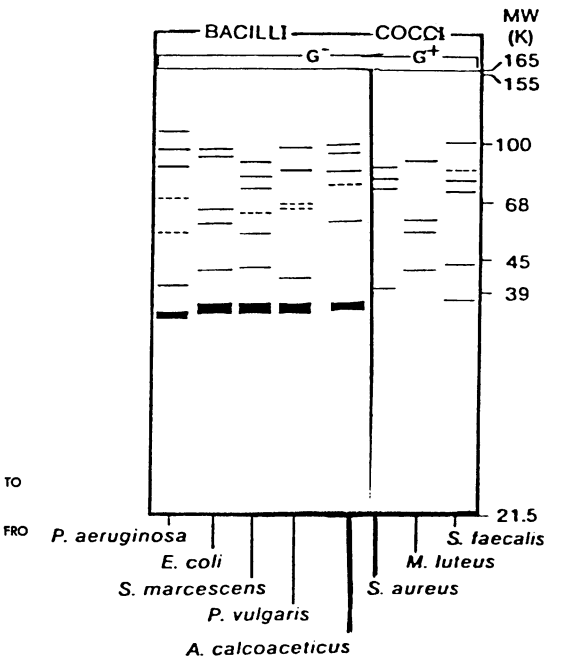

Fig. 1. Penicillin binding proteins of common Gram-positive and Gram-negative organisms

infections by the Center for Disease Control showed that methicillin-resistant *S. aureus* had reached levels of 10 to 20% in some hospitals. Was this resistance due to a new penicillinase? No, these isolates have altered PBPs, and penicillins and even cephalosporins do not readily kill such *S. aureus*. Certain *S. epidermidis* isolates also resist methicillin-nafcillin-cephalosporins by this same mechanism.

Gram-positive species such as *Streptococcus pneumoniae* were reported to be relatively resistant to penicillin G in 1977. These organisms do not possess β-lactamases, but have altered PBPs.[7] Unfortunately, to date no penicillin structures have been synthesized which will overcome this problem of altered PBPs, and hence penicillins are not effective against bacteria that possess different PBPs.

The development of such compounds as methicillin and oxacillin did not help against such Gram-negative bacteria as *E. coli*, *Klebsiella*, and *Pseudomonas*, which in the 1960s assumed major importance as the organisms causing infection in hospitalized patients. The reason for this was that these compounds did not readily pass through the outer wall of Gram-negative bacteria and did not reach the PBPs. Substitution on the

α-carbon of the hydrophobic side chain of benzylpenicillin with either an amino (ampicillin) or carboxyl (carbenicillin) group overcame this problem. Although in 1961, when ampicillin was introduced, 98% of *E. coli* were inhibited by readily achievable concentrations of ampicillin, this was not true in 1980, when only 60% of *E. coli* in a hospital were susceptible. This was the result of the presence of β-lactamases, again on plasmids, which resulted in destruction of these compounds.[5] Carbenicillin or ticarcillin were able to inhibit such organisms as *Pseudomonas* or *Enterobacter* because these organisms contained β-lactamases which acted primarily as cephalosporinases and these enzymes were actually to a slight degree inhibited by these compounds.[8] Nonetheless, the widespread appearance of plasmid-mediated β-lactamases (penicillinases) in organisms such as *E. coli, Salmonella, Shigella, Neisseria gonorrhoea,* and *Haemophilus influenzae* has limited to some extent the use of such drugs as ampicillin, ticarcillin, and related compounds (Table II).

A further chemical development in penicillins which occurred in the 1970s was the synthesis of the ureido penicillins — azlocillin, mezlocillin, and the piperazine agent piperacillin (Figure 2). These compounds have either a ureido or piperazine ring on the 9α carbon which causes them to be active against organisms such as *S. faecalis* (minimal inhibitory concentration — MICs 1-3 μg./ml.), whereas such carboxy penicillins as ticarcillin and carbenicillin have MICs of 25 μg./ml. against enterococci since the acidic function at position nine decreases binding to PBPs in this species. Such ureido penicillins as mezlocillin also inhibit about 50% of *Klebsiella pneumoniae*, which resist carbenicillin and ticarcillin because they more readily penetrate *Klebsiella* and bind to PBPs before they are destroyed by the β-lactamases present in these species.

It would be inappropriate to comment upon resistance mechanisms to penicillins without acknowledgment of the role of permeability to the compounds. This has been alluded to in the foregoing discussion of the reason for the failure of antistaphylococcal (β-lactamase-resistant) penicillins to inhibit Gram-negative species. Gram-negative bacteria have become resistant to penicillins substituted at the α-carbon by changing the cell envelope. This has occurred with *N. gonorrhoeae, Serratia, Enterbacter*, and, most important, with some *P. aeruginosa* resistant to the antipseudomonas penicillins. Table III shows the mechanisms of resistance of major bacterial groups to penicillins and Table IV shows the correlation of inhibitory levels of penicillins and the factors which affect the MIC and MBC levels. Table IV demonstrates how any one of these

TABLE II. β-LACTAMASE STABILITY OF VARIOUS PENICILLIN CLASSES TO MAJOR ENZYMES

	β-lactamase enzyme type			
Compound	*Ia*† *Enterobacter*	*Id*† *Pseudomonas*	*IIIa** *E. coli*	*IVc*† *Klebsiella*
	Relative rate of hydrolysis			
Penicillin G	100	100	100	100
Ampicillin	0	0	180	150
Carbenicillin	0	0	10	50
Cloxacillin	0	0	0	150
Mezlocillin	0	0	60	60
Piperacillin	0	0	70	50

*TEM enzymes, plasmid-mediated
†Chromosomal β-lactamases
Classification of β-lactamases is that of Richmond and Sykes.

factors causes change in either MIC or MBC concentrations in *S. aureus*, *E. coli*, and *P. aeruginosa*.

One further mechanism of resistance to penicillins is that of suppressed murein hydrolase activity.[7] Penicillin-tolerant isolates have been found in both Gram-positive species such as *Streptococcus sanguis* and *S. pneumoniae* and *E. coli* and *P. aeruginosa*. The types of hydrolytic activities which are defective in the tolerant mutants vary by species. The survival or death of such bacteria exposed to penicillin depends upon murein hydrolase activity. In some species the penicillin-induced secretion of lipid-teichoic acid and lipids of resistances pheno-typically expressed by major differences between inhibitory (MIC) and bactericidal (MBC) levels has been shown to be clinically important for *S. pneumoniae* causing meningitis and *S. aureus* causing endocarditis.

MECHANISMS TO OVERCOME BACTERIAL RESISTANCE

The search for molecules resistant to Gram-positive β-lactamases of staphylococci resulted in synthesis of molecules in which a carboycyclic or heterocyclic ring was attached directly to the carbonyl group substituting the amino group of 6-amino penicillanic acid (6-APA). More recent attempts at overcoming resistance in Gram-negative bacteria have been directed at finding agents which bind to different receptor sites in bacteria or in finding compounds which act as β-lactamase inhibitors.

Mecillinam is an amidino penicillin with poor affinity for PBPs of Gram-

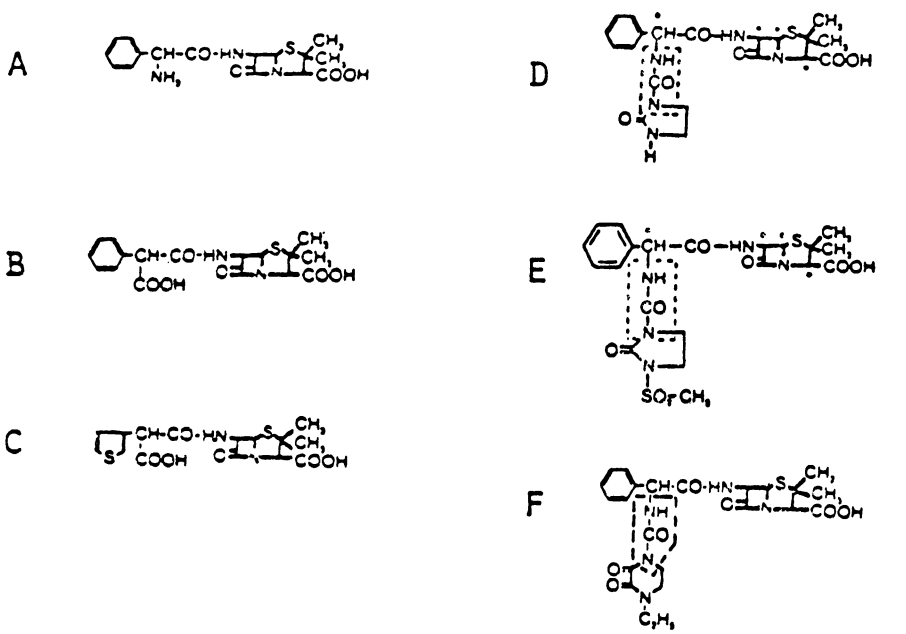

Fig. 2. A = ampicillin, B = carbenicillin, C = ticarcillin, D = azlocillin, E = mezlocillin, F = piperacillin

positive bacteria, but that binds selectively to the PBP 2 of certain Gram-negative species such as *E. coli, Klebsiella* or *Enterobacter,* but poorly to PBPs of *Proteus* or *Pseudomonas.*[2] It is destroyed by β-lactamases such as the TEM enzyme which is the plasmid enzyme found in *E. coli, H. influenzae, N. gonorrhoeae, Salmonella,* and *Shigella,* but the compound interestingly is less readily destroyed. That is, the Km is 10^{-4}M rather than 10^{-5}M and it readily goes through the outer wall to its PBP 2 receptor.[9,10] Thus this agent mecillinam will inhibit an organism resistant to ampicillin and carbenicillin (MIC > 400μg./ml.) at concentrations below 1μg./ml. Since this compound binds to PBP 2 and other penicillins bind to PBP lb and 3, it acts synergistically with other penicillins.[11]

Of greater importance are β-lactamase inhibitors such as clavulanic acid which is the prototype of these compounds.[12] The antistaphylococcal penicillins had been inhibitors of the β-lactamases found in such organisms as *Pseudomonas,* but the concept of combining a β-lactamase unstable and stable compound, for example ampicillin and cloxacillin, had proved clinically successful only when the concentrations of both agents were extremely high as occurred in the urine. This was of no value in infections in other parts

TABLE III. MECHANISMS OF RESISTANCE OF BACTERIA TO PENICILLINS*

Organism	*Mechanism*	*Penicillin*
Acinetobacter	β-lactamase	Carbenicillin-Ticarcillin
Aeromonas	β-lactamase	Ampicillin Carbenicillin*
Bacteroides fragilis	β-lactamase	Penicillin G Ampicillin Carbenicillin
	Permeability	Oxacillin
Bacteroides melaninogenicus	β-lactamase	Penicillin G
Escherichia coli	β-lactamase	Ampicillin Carbenicillin
Enterobacter cloacae	Permeability β-lactamase	Ampicillin Carbenicillin
Haemophilus influenzae	β-lactamase	Ampicillin
Klebsiella pneumoniae	β-lactamase	Ampicillin Carbenicillin Mezlocillin-Piperacillin
Neisseria gonorrhoeae	Permeability	Penicillin G
	β-lactamase	Ampicillin
	Altered PBP†	All penicillins
	Permeability	Ampicillin
Providencia	β-lactamase	Carbenicillin
Pseudomonas aeruginosa	Permeability β-lactamase	All agents Carbenicillin Mezlocillin-Piperacillin
Pseudomonas maltophilia	Permeability	All agents
Pseudomonas cepacia	β-lactamase	Carbenicillin
Salmonella	β-lactamase	Ampicillin
Shigella	β-lactamase	Ampicillin
Serratia	Permeability	All agents
	β-lactamase	Carbenicillin
Staphylococcus aureus	β-lactamase	Penicillin G
	Altered PBP	All agents
Staphylococcus epidermidis	β-lactamase	Penicillin G
	Altered PBP	All agents
Streptococcus faecalis	Permeability	Penicillin G
	PBP	Carbenicillin Oxacillin
Streptococcus pneumoniae	PBP	Penicillin G
Streptococcus viridans group	PBP	Penicillin G
Yersinia	β-lactamase	Ampicillin

*Drugs which are listed are listed are those which normally might be considered as a possible therapeutic agent. The notation of carbenicillin stands for ticarcillin as well. Mezlocillin and piperacillin are destroyed by β-lactamases but their ability to go through the outer wall and to bind to PBPs may overcome this in some *Klebsiella* or *Pseudomonas* except those which produce large amount of β-lactamase.

†PBP = penicillin-binding protein.

TABLE IV. CORRELATION OF INHIBITORY LEVELS OF PENICILLINS AND FACTORS — PERMEABILITY, β-LACTAMASE AND PENICILLIN-BINDING PROTEINS INVOLVED IN ACTIVITY OF COMPOUNDS

Organism	*Factors affecting activity*		*Penicillin-binding proteins*	*Type of penicillin*	*MIC*	*MBC*
	Permeability	*β-lactamase*				
S. aureus	−	−	Normal	Penicillin G	0.05	0.05
S. aureus	−	++++	Normal	Penicillin G	>256	>256
S. aureus	−	++++	Normal	Methicillin	1	2
S. aureus	−	++++	Altered	Methicillin	16	>256
E. coli	+	−	Normal	Ampicillin	2	4
E. coli	+	−	Normal	Methicillin	>256	>256
E. coli	+	++++	Normal	Ampicillin	>256	>256
Ps. aeruginosa	++	−	Normal	Carbenicillin	16	64
Ps. aeruginosa	++	+++	Normal	Carbenicillin	>256	>256
Ps. aeruginosa	++++	−	Normal	Carbenicillin	128	>256
Ps. aeruginosa	++	−	Altered	Piperacillin	4	>256

TABLE V. COMBINATION OF AMOXICILLIN + CLAVULANIC ACID OR TICARCILLIN + CLAVULANIC ACID

Organism	MIC, μg./ml			
	Amoxicillin	*Ticarcillin*	*Amoxicillin + Clavulanic acid**	*Ticarcillin + Clavulanic acid**
Staphylococcus aureus	>400	>400	0.1	0.4
Escherichia coli†	>400	>400	2	2
Klebsiella	>400	>400	4	2
Salmonella typhi†	>400	200	4	2
Shigella sonnei†	>400	200	4	2
Haemophilus influenzae†	25	25	0.1	0.1
Neisseria gonorrhoeae†	25	25	0.1	0.1
Pseudomonas aeruginosa†	>400	>400	100	8
Acinetobacter†	>400	>400	100	8
Enterobacter cloacae†	>400	>400	100	16
Providenica†	>400	>400	100	8
Bacteroides fragilis	>400	64	64	8

*Clavulanic acid lμg./ml.
†These isolates contain the TEM β-lactamase (Richmond IIIa)

of the body, and resistance readily developed to the combination. Clavulanic acid is a compound which has the ability to combine with β-lactamases and, after an initial brief period in which it functions as a competitive inhibitor of the enzyme, it begins to undergo destruction. This is unfortunate for the β-lactamase enzyme because in effect the breakdown of clavulanic acid acts as a suicide molecule destroying the enzyme.

Clavulanic acid acts synergistically with ampicillin or amoxicillin to inhibit β-lactamases of *S. aureus* and the plasmid enzymes of the TEM type in *E. coli*, *Haemophilus*, and *Neisseria* (Table V).[12] It also acts against the enzymes of *Klebsiella* and *Bacteroides fragilis*. Unfortunately, clavulanic acid and the other β-lactamase inhibitor, sulbactam, do not inhibit β-lactamases that act primarily as cephalosporinases.[13] Hence they do not make ampicillin active against *Morganella*, *Serratia*, *Enterobacter*, and *P. aeruginosa*. In essence, combination of clavulanic acid and amoxicillin (Augmentin) makes a complex which has the properties of both a penicillin and a cephalosporin. Combination of clavulanic acid with the antipseudomonas penicillins, such as ticarcillin or piperacillin, yields drugs of exceedingly large spectrum covering virtually all Gram-positive cocci and important Gram-negative species such as *Klebsiella*, resistant *Pseudomonas* and those *Morganella*, *Citrobacter*, and *Acinetobacter* which were resistant because of the presence of a β-lactamase.[14]

Pharmacokinetic Considerations of Penicillins

Penicillins differ remarkably in their pharmacologic properties.[15] Penicillin G is not acid stable and as a result penicillin V has become the oral preparation of common use because it is well absorbed, even when ingested with food. Cloxacillin and dicloxacillin, antistaphylococcal agents, are both well absorbed when given orally, but the physician should realize that the better absorption of dicloxacillin is nullified by its greater protein binding. Although a level of 40μg./ml. could be achieved with 500mg. of dicloxacillin compared to 20μg./ml. after 500mg. of cloxacillin, the dicloxacillin is 98% protein bound so the free level of drug, active component of cloxacillin is 0.8μg./ml. since it is 96% protein bound.

Differences in absorption are significant for some aminopenicillins. Amoxicillin is twice as well absorbed as ampicillin and the ester of ampicillin, bacampicillin, also is extremely well absorbed, yielding very high blood levels of free ampicillin.

All of the penicillins are well distributed to various body compartments and only in the cerebrospinal fluid and eye are levels of the penicillin compounds poor. In the presence of meningitis cerebrospinal fluid levels, the levels of penicillins such as penicillin G and ampicillin are 5 to 15% of the serum levels. This usually is adequate for such Gram-positive species as *S. pneumoniae* or group B streptococci and for *N. meningitidis* and *H. influenzae* but inadequate for *Enterobacteriaceae* and *Pseudomonas*.

Because penicillins are readily secreted by renal tubules, their persistence in serum is brief. Indeed, the serum half-life of penicillin G in only 30 minutes and of carbenicillin and ticarcillin one hour. Tubular secretion provides excellent urine levels. The important aspect in urinary infection is that even when renal function has fallen to levels as low as glomerular clearance rates of 10 to 15ml./min., the urine levels of drug are adequate to inhibit most bacteria.

Penicillins accumulate in the body to varying degrees in renal failure so that the half-life of penicillin G increased to only three or four hours, whereas the half-life of carbenicillin or ticarcillin will be 12 to 18 hours in patients with creatinine clearance <5ml./min.

Pharmacokinetics of penicillins differ in certain patient groups, and it is important to keep this in mind when using these agents. In the newborn, particularly low weight infants, extravascular volume is increased and renal function decreased since full tubular secretion has not yet developed. Thus, larger doses on a mg./kg. basis are needed to achieve the same serum levels,

but the time between doses is prolonged. Children with pulmonary cystic fibrosis also are different. They excrete all of the penicillins at increased rates by both renal and hepatic mechanisms. Hence these children, who also because of body habitus have an increased extravascular space, need larger doses more frequently than do other patients. Finally, both ticarcillin and carbenicillin accumulate in renal failure and these agents have further prolongation of half-life if there is concomitant hepatic failure with elevated bilirubin levels. An example would be a ticarcillin serum half-life of one hour in a patient whose creatinine clearance is >90ml./min., half-life of 15 hours if the creatinine clearance is <7ml./min., and half-life of 30 hours if creatinine clearance <7ml./min. and bilirubin >10mg./dL.

Toxicity Considerations

Allergy to penicillins due to IgE mechanisms is well known, but many individuals have rashes after receiving ampicillin who are not truly allergic to penicillins. These patients could receive the drugs again if needed.

Several things about ticarcillin and carbenicillin are important to remember. These agents are disodium salts containing approximately 5mEq. sodium per gram of drug. The compounds are anions, and as such are removed by the kidney. This large load of nonreabsorbable anion can alter $(H)^+$ transport in the distal tubule and thereby promote potassium loss which can result in severe consequences. The agents also can at high serum concentrations inhibit platelet contraction and hence provoke bleeding.[16] An uncommon but important aspect of these latter two agents is their interaction with aminoglycosides to inactivate the aminoglycoside. This reaction is uncommon in the human body and most likely to occur if the agents have been inadvertently mixed in the same intravenous bottle. The reaction occurs least often with amikacin. But inactivation can occur in the presence of renal failure if the carbenicillin or ticarcillin accumulate and thus produces high concentrations to inactivate the gentamicin or tobramycin.

Clinical Considerations

Penicillins remain the drugs of choice in most infections if the patient is nonallergic. They are safe, effective, and cure infections even if the patient's host defenses are depressed. It is best to analyze the use of penicillins by disease entity rather than to take them by group.

Upper respiratory tract infections remain an area of major use of penicillins. Penicillin G is still the preferred therapy of streptococcal pharyngitis

administered as the benzathine salt or as oral penicillin V. In contrast, in both otitis media and sinusitis, amoxicillin has proved extremely effective because it is active against the primary pathogens, *S. pneumoniae, H. influenzae,* and *S. pyogenes,* which are involved in these illnesses.

Surprisingly, penicillin G remains the drug of choice to treat outpatient pneumonitis, which most often is due to *S. pneumoniae.* Indeed, 600,000 units intramuscularly twice daily is still an excellent regimen. Penicillin V is a superior therapy for outpatient aspiration pneumonia. In contrast, aspiration in the hospital may sometimes be better treated with ticarcillin if *Pseudomonas* plus anaerobic species are involved or with cefoxitin if *Klebsiella* is the culprit.

Penicillin G is still the best form of therapy of streptococcal endocarditis, whether streptococci are of the *viridans* group or *S. bovis.* Whether ampicillin is better against *S. faecalis* is debatable.

Antistaphylococcal penicillins are useful in all of the infections produced by this organism, whether pneumonia, endocarditis, osteomyelitis, or skin infections.

Meningitis due to *S. pneumoniae* or *N. meningitidis* is best treated with penicillin G, while ampicillin is quite effective against most *H. influenzae* which do not possess β-lactamases, and it also is the drug of choice for *Listeria monocytogenes.* In fact, penicillin remains an important agent to treat nonmeningeal nervous systemic infections such as brain abscess, subdural and epidural empyema, since streptococci are so often a component of these infections.

In spite of earlier comments upon resistance mechanisms, ampicillin or amoxicillin as single dose therapy are quite effective treatment of gonorrhea and of lower urinary tract infections since the latter are due primarily to ampicillin-susceptible *E. coli.*

Where do such new agents as ticarcillin, mezlocillin, and piperacillin belong in this classification of use of penicillins? As noted previously, the compounds may provide some benefit in hospital-acquired pneumonitis and can be viewed as essential when *Pseudomonas* is involved. The agents are extremely important in the therapy of an uncommon but increasingly recognized disease—necrotizing otitis.[17] This illness is seen in elderly diabetic patients who complain of intense pain in the ear and are found to have an extensive inflammatory response of the external auditory canal progressing into adjacent bony structures. The antipseudomonas penicillins have proved lifesaving in burn patients in whom sepsis due to *Pseudomonas* is common.[18]

Less clear is the role of such agents in therapy of abdominal and gyneco-

logic infections. These infections usually are of mixed bacterial origin, aerobic and anaerobic. Studies comparing the efficacy of ticarcillin plus gentamicin versus chloramphenicol or clindamycin plus gentamicin have shown equivalent therapeutic cures.[19] The development of the new so-called "third-generation" cephalosporins provides another possible group of compounds for such infections. Data are not yet sufficient to show what is the best compound or combination to utilize in these surgical infections.

Lastly, the compounds have proved to be extremely helpful in the therapy of febrile neutropenic patients.[20] In this setting the compounds are combined with an aminoglycoside. Toxicity has been low.[21] Studies of the newest agents of this group of penicillins, namely, mezlocillin and piperacillin, have demonstrated that even though these agents inhibit 50 to 60% of *Klebsiella*, the agents cannot be used as single therapy.[22] It is also of note that comparison of ticarcillin plus amikacin versus piperacillin plus amikacin showed no major improvement in survival or decrease in toxicity of the piperacillin versus the ticarcillin.

It will undoubtedly take several years to sort out where each of the drugs such as azlocillin, carbenicillin, mezlocillin, piperacillin, and ticarcillin should be used. At present all have been shown to be effective therapy of serious infections in the hands of skilled clinical investigators. However, the largest experience has been with ticarcillin used in combination with aminoglycosides.[18-20]

SUMMARY

Marked progress in the development of penicillins over the past decade has led to better understanding of the activity and resistance mechanisms operative when penicillins attack bacteria. Penicillins remain the drugs of choice for many common outpatient infections where they can be used in oral forms as penicillin V, amoxicillin, or cloxacillin. As parenteral agents, ampicillin and ticarcillin have proved their importance in the past decades. The advent of new penicillins such as mecillinam, mezlocillin, and piperacillin adds other agents to our armamentarium. During the next decade we shall learn not only how to use these agents, but where the β-lactamase inhibitors such as clavulanic acid should be used.

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